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During the study of C-O cleavage reaction toward the synthesis of Eleutherobin analogues, wehave discovered a novel functionalization of α,β-epoxy ketone. This reaction seems to be veryuseful in preparation of vinyl functionalized allylic alcohol. Modification of hydrazinereactant is now being under investigation. On the other hand, coupling of two key fragmentsfor the intramolecular Diels-Alder reaction failed under conventional reaction condition andthe suitable reaction condition is now being studied.

**15. SUBJECT TERMS**
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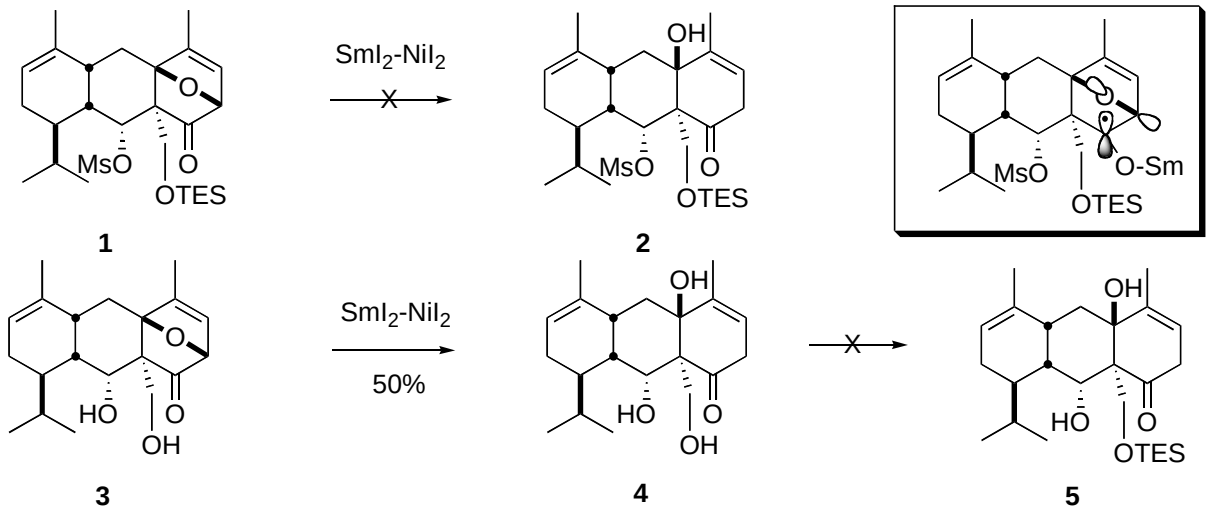
## 1. Introduction

The development of an efficient synthetic route to Eleutherobin and its analogues has been recognized as a daunting task for synthetic communities. Its scarce availability in nature and potent toxicity against cancer has attracted our attention and led us to study the synthesis of Eleutherobin utilizing a tandem Diels-Alder reaction and Grob-fragmentation strategy. During the second year of the grant, we studied the problematic C-O bond cleavage reaction using hydrazine and discovered a novel chemical transformation, which could be a powerful source of highly functionalized allylic alcohols.

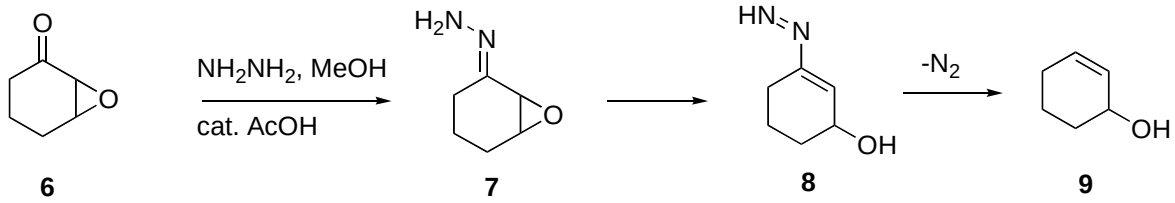
## 2. Body

Previously, we have successfully prepared the advanced intermediate **1**, which could become a substrate for the Grob fragmentation after C-O bond cleavage. Unfortunately, cleavage of the C-O bond failed as it was extremely resistant to the $SmI_2$ reduction condition. Treatment of **1** to Zn-AcOH condition also failed to produce the desired Grob substrate **2**. This issue may be related with the orbital alignment of the ketyl radical anion as depicted in **Scheme 1** or an initial electron transfer process.[1)] Thus, successful implementation of $SmI_2$ reduction to triol **4** was only achieved when diol **3** was subjected to the same reaction condition.[2)] However, further attempts to transform triol **4** to the Grob fragmentation substrate **5** were unsuccessful due to facile retro-aldol reaction. We then turned our attention to other C-O bond cleavage reactions. We believed that a Wharton rearrangement could provide a possible solution.



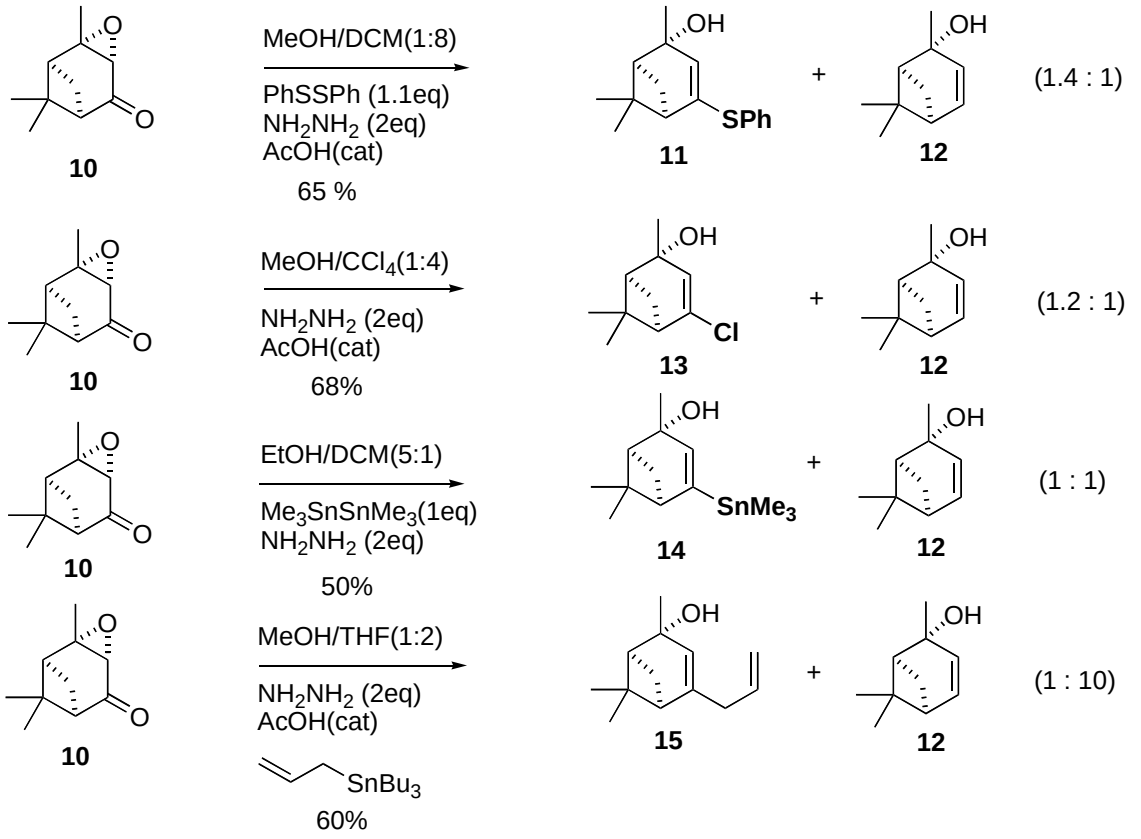

**Scheme 1**. Failure to preparation of Grob fragmentation substrate **2**

As shown in **Scheme 2**, the Wharton rearrangement can transform α, β-epoxy ketone **6** to allylic alcohol **9**.



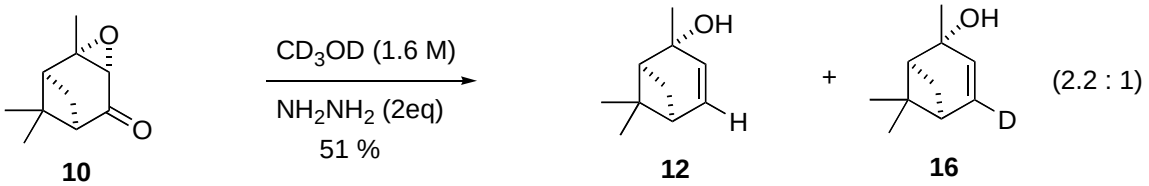

**Scheme 2.** Wharton Rearrangement

In our study, simple application of the Wharton rearrangement would only lead to the formation of diene alcohol that is not suitable for our purpose to retain the original carbonyl functionality. However, according to the reaction mechanism proposed by G. Stork *et al*, the intermediate of the Wharton rearrangement could be vinyl radical species from the release of nitrogen gas in vinyl diazene **8**.[4] We envisioned that this intermediate could be functionalized at the vinylic position if a suitable radical trapping agent is added. The resulting product would be a vinyl functionalized allylic alcohol which could be converted into carbonyl group again. Thus, we set to test our hypothesis with epoxy ketone **10** which can be readily prepared from verbenone.




**Scheme 3**. Wharton functionalization of epoxy ketone **10**

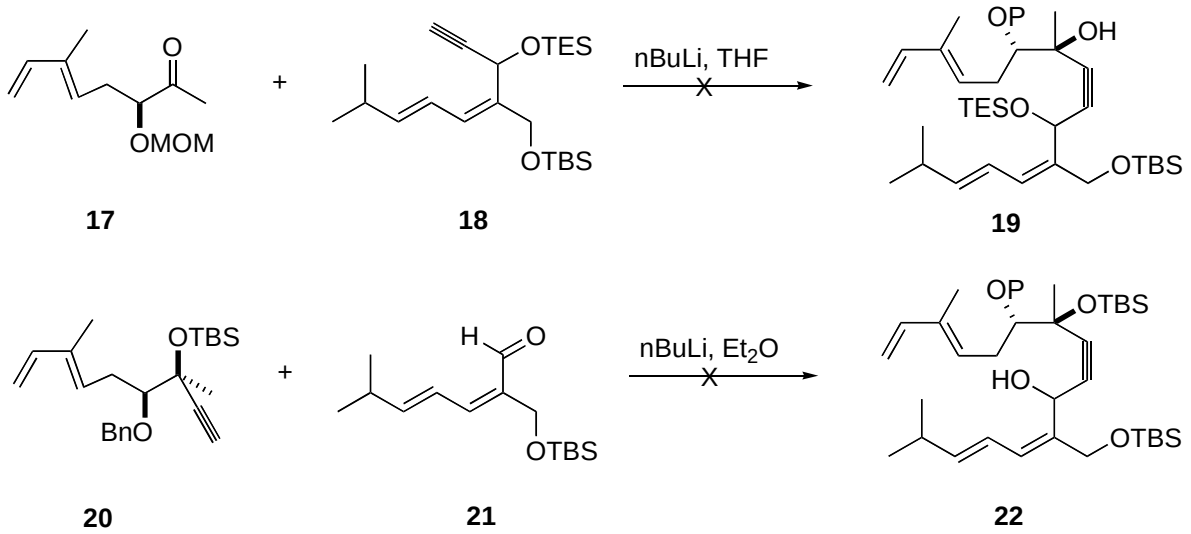
After much experimentation on the reaction condition, our hypothesis proved to be true. Vinyl sulfide **11**, vinyl halide **13** and vinyl tin species **14** could be prepared in a single pot operation in a good to moderate yield. More importantly, vinyl halide **13** and vinyl tin species **14** could be utilized in Palladium mediated C-C bond forming reactions, which further reinforces the importance and versatility of this transformation. Furthermore, formation of the 1,4 diene **15** indicates the direct C-C bond formation could be possible. Thus, this novel Wharton functionalization is extremely versatile as it provides a direct method to prepare vinyl functionalized allylic alcohols in a facile manner. However, one limitation is the formation of the normal Wharton reaction product **12**. This issue led us to investigate the source of the hydrogen atom. We ran the reaction in the $CD_3OD$ without the trapping agent as shown in **Scheme 4**. Surprisingly, deuteriated allylic alcohol was not the predominant product which suggests hydrazine itself could be the main source of the hydrogen atom.




**Scheme 4**. Quenching study of Wharton reaction

Thus, it is conceivable that use of monosubstituted hydrazine would prevent the formation of the normal Wharton product. Currently, we are investigating the use of a monosilylated hydrazine. [5)] If successfully implemented, this method would become very influential in the synthetic community due to its versatility and simplicity.

On the other hand, we also prepared the two key fragments for the intramolecular Diels-Alder approach as proposed in the previous annual report.




**Scheme 5**. Attempted preparation of Diels-Alder reaction substrate **19** or **22**

As shown in **Scheme 5**, conventional condition utilizing *n*-BuLi as a base was not successful in the preparation of the desired Diels-Alder substrate **19** as only starting materials were recovered. This suggested thatthe generation of alkynyl anion failed. Likewise, addition of alkyne **20** into aldehyde **21** was also unsuccessful. The only product obtained was *n*-BuLi addition to aldehyde **21**. Thus, deprotonation conditions of terminal alkyne **17** or **20** are now being studied.

**3. Key Research Accomplishment**

- Discovery of a Wharton functionalization
- Determination of the role of hydrazine as the main hydrogen atom source in the Wharton reaction

**4. Reportable outcomes**

Poster presentation
"Synthetic studies on the Taxol-like cancer chemotherapeutic agent"
Innovative Minds in Prostate Cancer Today (IMPaCT) meeting, Atlanta, GA, Sep 2007

Manuscript on Wharton functionalization in preparation

**5. Conclusion**

During the second year of this grant, we have discovered a novel and powerful chemical transformation in studying the C-O bond cleavage reaction. This reaction would lead to a number of synthetically useful

intermediates and give further insight on the traditional Wharton reaction. Attempted assembly of the two key fragments for the intramolecular Diels-Alder reaction revealed that more extensive studies would be needed for the deprotonation reaction condition.

"So What?"

As a result of the work done over the past year, a highly useful novel transformation was discovered in the course of study on the C-O cleavage reaction. This Wharton functionalization could be very powerful tool in the synthetic community if combined with organometal catalyzed C-C bond forming reactions.

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**7. Appendices**

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